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# Benz[*f*]tryptophan, a Bathochromic Analog of Tryptophan, Synthesis of its N-α-*t*-Boc Derivative.

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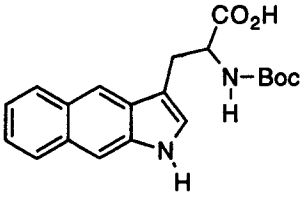
***Abstract:*** The recently reported anionic cyclization of N,N-diallylaminobenzene derivatives to indolines is readily extended to the synthesis of a naphthalene derivative which is taken on to the first synthesis of a benz[*f*]tryptophan derivative. © 1997 Elsevier Science Ltd.

Tryptophan is the most red-shifted of the natural amino acid fluorophores, thus its fluorescence can be studied even in complex protein environments containing several tyrosine and phenylalanine residues. However, multiple tryptophan residues can cause difficulties particularly for the application we are planning. We are developing tryptophan analogs as fluorescent probes of peptide hormone structure and dynamics in complex environments such as peptide hormones in receptor sites.[1] Peptide hormones are typically flexible molecules in solution, but adopt unique conformations upon receptor binding. The selectivity of fluorescence spectroscopy should allow us to focus on peptide hormone structure even while bound in receptor sites. We hope that this information can be used to rationally design more active constrained peptide hormone analogs. To address this need, we have designed a tryptophan analog with an absorbance and emission expected to be red-shifted from the natural amino acids. Herein, we report the synthesis of N-α-*t*-Boc-benz[*f*]tryptophan, **1**, a fluorescent amino acid probe suitably protected for incorporation via solid-phase peptide synthesis.

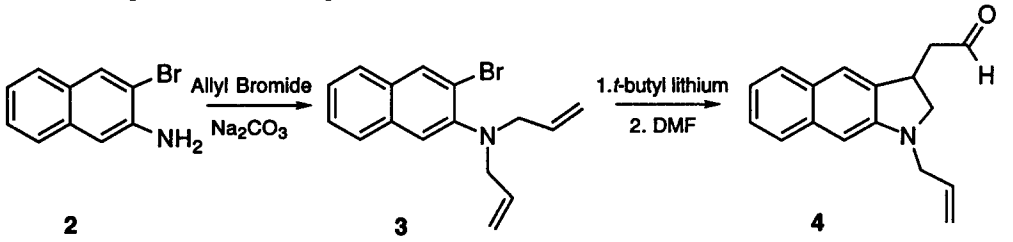



**1**

As compared to the other benzannulated tryptophan derivatives: benz[*g*]tryptophan and benz[*e*]tryptophan, benz[*f*]tryptophan best mimics the structure of tryptophan and should be the least perturbing of native peptide structure Unfortunately, the electronic directing effects of the naphthalene

moiety makes the synthesis of the benz[*f*]tryptophan the most difficult of the benzannulated tryptophans.[2] Low benz[*f*]indole yields hinder benz[*f*]tryptophan synthetic routes known to convert indole to tryptophan, but fluorescence experiments comparing benz[*f*]indole with indole suggest that benz[*f*]tryptophan is likely to be an excellent fluorescence probe.[3]

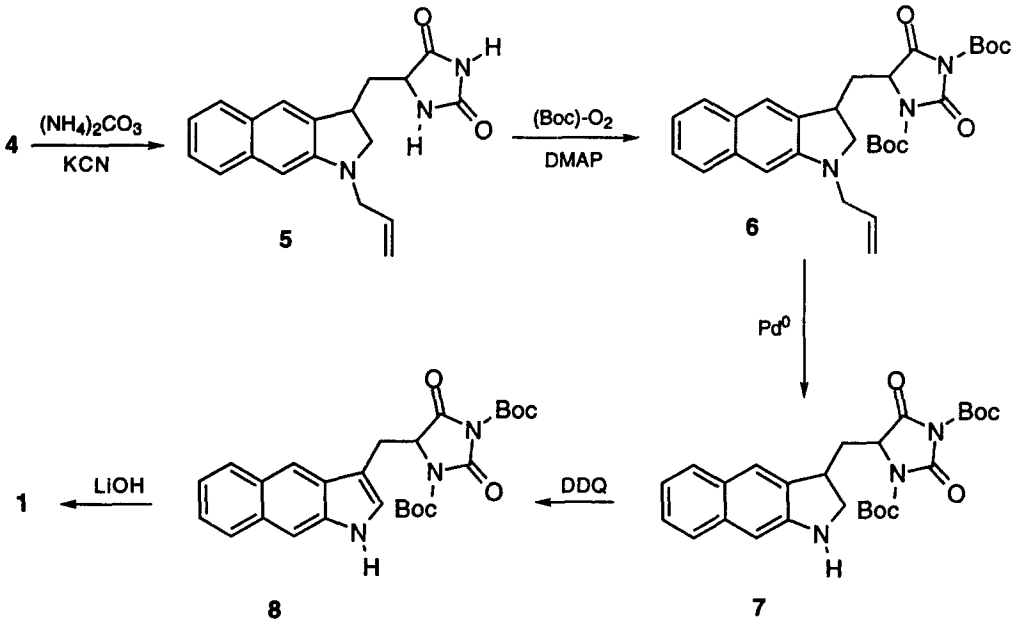
The N,N-diallyl derivative of 3-bromo-2-aminonaphthalene, **2**,[4] is generated by refluxing **2** with 8 equiv. of allyl bromide and excess sodium carbonate in N,N-dimethylformamide (DMF) to yield **3**.[5,6] The indoline backbone is formed via an anionic cyclization of **3**. The cyclization is done by treating **3** with 2.2 equiv. of *t*-butyllithium at -78° C in *t*-butyl methyl ether (TBME) for 1 hour and warming to room temperature for 15 minutes.[5] The solution is cooled back to -78° C, 3 equiv. of DMF are added, and the resulting mixture is allowed to warm to room temperature.[6] The organic solution is washed with 10% $NH_4Cl$ solution and the aldehyde, **4**, is isolated. As expected, the anionic cyclization failed to take place unless the temperature is raised.[5,6]




**2** **3** **4**

**4** is converted to its corresponding hydantoin using modified Bucherer-Bergs conditions; 3 equiv. of KCN, 3 equiv. of $(NH_4)_2CO_3$ in a 1:1:1 mixture of methanol:tetrahydrofuran (THF):water with heating to 60° C for 4 days.[7,8,9] Purification over silica gel (7:3 ethyl acetate:hexanes) yields pure hydantoin **5** (49% from 2-bromo-3-aminonaphthalene) (mixture of diasteromers confirmed by NMR). Logically, the next step in the synthesis would be the removal of the allyl protecting group followed by oxidation to the indole. We found that after removal of the allyl group, the resulting hydantoin is only sparingly soluble in organic media. Therefore, we activate the hydantoin nitrogens with *t*-butyloxycarbonyl (Boc) to allow mild hydrolysis of the hydantoin (discussed later) and to alleviate the solubility problem. The hydantoin is treated with 3 equiv. of $(Boc)_2$-O and a catalytic amount of 4-N,N-dimethylaminopyridine (DMAP) in acetonitrile for 4 hours to yield protected hydantoin, **6** (89%).[7,8] The allyl protection of the indoline nitrogen is removed by refluxing with $Pd^0$ (tris(dibenzylideneacetone)-dipalladium(0)), 1,4-bis(diphenylphosphino)butane and thiosalicyclic acid (used as a proton source and a cation scavenger) in dry THF according to the procedure of Genêt and coworkers (54%).[10] The air sensitive indoline, **7**, is purified over silica gel ($CHCl_3$:hexanes:THF, 6:3:1) and immediately oxidized. The oxidation of the indoline is done by treating **7** with 1 equiv. of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in TBME for 1 hour to give indole, **8** (51%). Hydrolysis of hydantoins normally requires harsh conditions which may effect other functionalities in the molecule. We adapted a procedure developed by Rebek and coworkers for the mild hydrolysis of

hydantoins by first activating the hydantoin nitrogens with the Boc groups followed by treatment with mild base to hydrolyze the hydantoin.[11] The Boc protected hydantoin is treated with 8 equiv. of 1N LiOH and THF as a co-solvent for 24 hours to give the N-α-*t*-Boc-benz[*f*]tryptophan,[12] **1**, after work-up (50%).[7,8,11]




We expected to obtain the free amino acid upon hydrolysis of the protected hydantoin, **8**, with LiOH based on previous reports in the literature and results from our laboratory.[7,8,11] However, only α,α–disubstituted hydantoins had previously been reported to undergo this facile hydrolysis to the free amino acid, while hydantoin, **8**, is only mono-substituted.[7,8,11] This is a fortunate discovery since **1** is already suitably protected for incorporation into a peptide via solution or solid-phase peptide synthesis. We postulate that the hydrolysis proceeds via a different mechanism for mono- and α,α–disubstituted hydantoins. Mechanistic studies are currently underway to address this issue and will be reported shortly.

This synthesis demonstrates that the anionic cyclization of N,N-diallylaminobenzene derivatives to indolines independently developed by Liebeskind, Bailey and coworkers is readily extended to the synthesis of a naphthalene derivative. Interestingly, we also observed that the mild hydrolysis of the intermediate mono-substituted, bis-Boc-hydantoin yields the N-α-*t*-Boc protected amino acid, whereas, the mild hydrolysis of α,α–disubstituted bis-Boc-hydantoins give the free amino acids. Additionally, we have reported the synthesis of a fluorescent amino acid probe that can be

incorporated into a peptide without severly altering peptide backbone conformation. This synthesis gives the racemic amino acid, but we do not require the resolved amino acid to perform preliminary experiments on the photophysics and fluorescence quenching of the free amino acid. Preliminary experiments show that the benzannulation shifts the absorbance and emission ~50 nm to the red from the parent indole chromophore.

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12. **1**, N-α-*t*-Boc-benz[*f*]tryptophan. $^1$H NMR (400 MHz, DMSO-*d*6) δ 10.88 (s, 1H), 8.06 (s,1H), 7.89 (m, 2H), 7.81 (s, 1H), 7.41 (s, 1H), 7.30 (m, 2H), 4.24 (dd, 1H), 3.29 (dd, 1H), 3.10 (dd, 1H), 1.31 (s, 9H). $^{13}$C NMR (100 MHz, DMSO-*d*6) δ 174.07, 155.23, 136.98, 129.81, 129.43, 128.18, 127.89, 127.50, 127.19, 122.94, 121.87, 115.27, 109.69, 77.75, 54.76, 28.20, 27.15. FAB-MS (glycerol) *m/z* 354.3 $(M)^+$; HRMS (*m*-nitrobenzyl alcohol) *m/z* 354.1552 (calcd. for $C_{20}H_{22}N_2O_4$, 354.1579).

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